REMARKS

Upon entry of the present amendment, claims 1-41 have been canceled, claims 42-67 have been added and claims 42-67 are pending. Substitute pages of the claims as amended and without brackets and underlining are attached.

Information Disclosure Statement

A Supplemental Information Disclosure Statement will be submitted under separate cover citing references found in other subject matter related applications. The full citation of the Fisher reference will be provided with that submission.

Specification

Provided herewith is an Abstract on a separate page for insertion into the application. Further, the first line of the application has been amended as suggested to make a proper claim for priority.

Rejections under 35 USC 112

Applicants respectfully submit that the rejections of claims 1-10 and 12-40 have been obviated as these claims have been canceled and replaced with the claims provided herewith.

Rejections under 35 USC 103

Applicants respectfully submit that the claims as amended are not obvious in view of EP330026. The structure defined in the claims provided herewith are not described or suggested by the '026 reference. The '026 reference describes compounds possessing anticholinesterase activity. Hence, one of ordinary skill in the art would have no motivation or reasonable expectation that compounds described in the '026 reference could be selected, modified and be used as anti-cancer agents as claimed.

Double Patenting

Amendments filed herewith and amendments to be filed in serial number 09/216,075 obviate and will obviate further the double patenting rejections.

Experimental Data

As further support of enablement for the claimed invention, submitted herewith is a list of compound and their pharmacological data.

Conclusions

In view of the above amendments and remarks, applicant respectfully requests allowance of the pending claims.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

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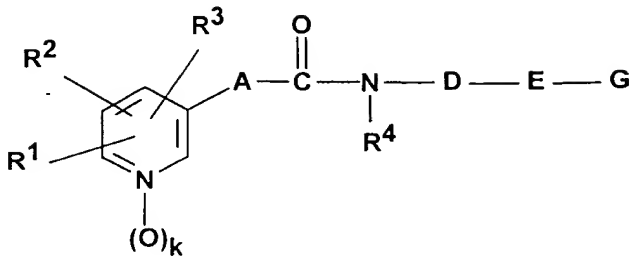
Claims

42. A compound of formula (I)



(I)

wherein:

R^1 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, C_3-C_8-cycloalkyl, C_1-C_4-hydroxyalkyl, hydroxy, C_1-C_4-alkoxy, benzyloxy, C_1-C_4-alkanoyloxy, C_1-C_4-alkylthio, C_2-C_5-alkoxycarbonyl, aminocarbonyl, C_3-C_9-dialkylaminocarbonyl, carboxy, phenyl, phenoxy, pyridyloxy, and NR^5R^6, wherein

R^5 and

R^6 are selected independently from each other from hydrogen and C_1-C_6-alkyl,

R^2 is selected from hydrogen, halogen, C_1-C_6-alkyl, trifluoromethyl and hydroxy,

wherein

R^1 and **R^2**, in the case they are adjacent, optionally form a bridge which is selected from $-(CH_2)_4-$, $-(CH=CH)_2-$ and $-CH_2O-CR^7R^8-O-$, wherein

R^7 and

R^8 are, independent from each other, hydrogen or C_1-C_6-alkyl,

R^3 is selected from hydrogen, halogen and C_1-C_6-alkyl,

R^4 is selected from hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, hydroxy, C_1-C_6-alkoxy and benzyloxy,

k is 0 or 1,

A is selected from

C_2-C_6-alkenylene, which is optionally substituted one to three-fold by C_1-C_3-alkyl, hydroxy, fluorine, cyano, or phenyl,

C_4-C_6-alkadienylene, which is optionally substituted once or twice by C_1-C_3-alkyl, fluorine, cyano, or phenyl,

1,3,5-hexatrienylene, which is optionally substituted by C_1-C_3-alkyl, fluorine, or cyano, and

ethinylene,

D is selected from

C_1-C_{10}-alkylene, optionally substituted once or twice by C_1-C_3-alkyl or hydroxy,

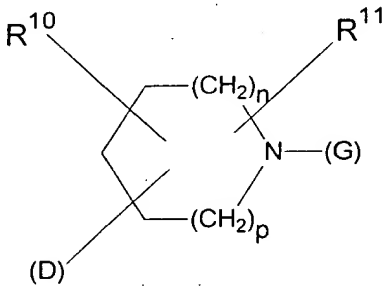
C_2-C_{10}-alkenylene, optionally substituted once or twice by C_1-C_3-alkyl or hydroxy, wherein the double bond optionally is to ring E,

C_3-C_{10}-alkinylene, optionally substituted once or twice by C_1-C_3-alkyl or hydroxy, and

the group consisting of C_1-C_{10}-alkylene, C_2-C_{10}-alkenylene and C_3-C_{10}-alkinylene, wherein one to three methylene units are isosterically replaced by O, S, NR^9, CO, SO or SO_2, wherein

R^9 is selected from hydrogen, C_1-C_3-alkyl, C_1-C_6-acyl and methanesulfonyl,

E is



(E1),

wherein

n and **p** are, independent of each other, 0, 1, or 2, with the proviso that **n** + **p** = 2,

R^{10} is selected from hydrogen, C_1-C_3-alkyl, hydroxy, hydroxymethyl, carboxy and C_2-C_7-alkoxycarbonyl,

R^{11} is hydrogen or an oxo group adjacent to the nitrogen atom,

G is selected from hydrogen,
G1, **G2**, **G3**, **G4** and **G5**, wherein

G1 represents the residue

$$-(CH_2)_r-(CR^{13}R^{14})_s-R^{12} \qquad (G1)$$

wherein

r is 0, 1 or 2, and

s is 0 or 1,

R^{12} is selected from

hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_3-C_8-cycloalkyl,

benzyl, phenyl,

the group consisting of monocyclic aromatic five- and six-membered heterocycles, which contain one to three hetero-atoms selected from N, S and O and are either bound directly or over a methylene group,

the group consisting of anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein the bond occurs either over an aromatic or a hydrogenated ring and either directly or over a methylene group, and

the group consisting of anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring atoms are selected from N, S and O and

the bond occurs either over an aromatic or a hydrogenated ring, and either directly or over a methylene group,

R^{13} has the same meaning as **R^{12}**, but is selected independently thereof,

R^{14} is selected from

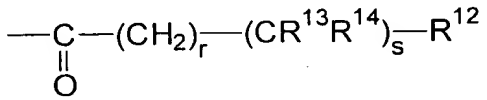
hydrogen, hydroxy, methyl, benzyl, phenyl,

the group consisting of monocyclic aromatic five- and six-membered heterocycles, which contain one to three hetero-atoms selected from N, S and O and are bound either directly or over a methylene group,

the group consisting of anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein the bond occurs either over an aromatic or a hydrogenated ring and either directly or over a methylene group, and

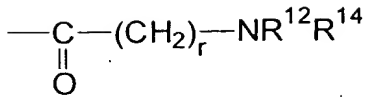
the group consisting of anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring atoms are selected from N, S and O and the bond occurs either over an aromatic or a hydrogenated ring and either directly or over a methylene group,

G2 is selected from



(G2a)

and



(G2b),

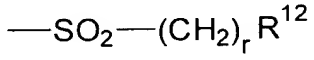
wherein R^{12} and R^{14} have the above meaning, or the group

is a nitrogen-containing heterocycle bound over the nitrogen atom, the nitrogen-containing heterocycle being selected from

the group consisting of saturated and unsaturated monocyclic, four- to eight-membered heterocycles, which, aside from the essential nitrogen atom, optionally contain one or two further hetero-atoms selected from N, S and O, and

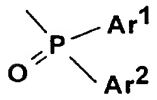
the group consisting of saturated and unsaturated bi- or tricyclic, anellated or bridged heterocycles with 8 to 16 ring atoms, which, aside from the essential nitrogen atom, optionally contain one or two further hetero-atoms selected from N, S and O,

G3 is the residue



(G3),

G4 is the residue



(G4),

wherein

Ar^1 and

Ar^2 are selected independently of each other from phenyl, pyridyl and naphthyl,

G5 is the residue

(G5),

wherein

R^{15} is selected from trifluoromethyl, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy and benzyloxy,

wherein aromatic ring systems in the substituents R^1, R^2, R^4, R^{12}, R^{13}, R^{14}, R^{15}, Ar^1 and Ar^2 and in the ring system -$NR^{12}R^{14}$ optionally carry independently of each other one to three substituents which are independently selected from the group consisting of halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, C_3-C_8-cycloalkyl, phenyl, benzyl, hydroxy, C_1-C_6-alkoxy, which is optionally entirely or partially substituted by fluorine, benzyloxy, phenoxy, mercapto, C_1-C_6-alkylthio, carboxy, C_1-C_6-alkoxycarbonyl, benzyloxycarbonyl, nitro, amino, mono-C_1-C_6-alkylamino, and di-(C_1-C_6-alkyl)-amino, wherein two adjacent groups of the aromatic ring or ring system optionally form an additional ring over a methylenedioxy bridge,

stereoisomers and/or mixtures thereof and pharmacologically acceptable acid addition salts

with the exception of (E)-3-(3-pyridyl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide hydrochloride.

43. A compound according to claim 42, wherein:

R^1 is selected from hydrogen, halogen, cyano, methyl, trifluoromethyl, hydroxy, C_1-C_4-alkoxy, ethylthio, methoxycarbonyl, tert-butoxycarbonyl, aminocarbonyl, carboxy, and phenoxy,

R^2 is selected from hydrogen, halogen, trifluoromethyl and hydroxy,

R^3 is hydrogen or halogen,

R^4 is selected from hydrogen, C_1-C_3-alkyl, hydroxy and C_1-C_3-alkoxy,

k is 0 or 1,

A is selected from C_2-C_6-alkenylene, optionally substituted once or twice by C_1-C_3-alkyl, hydroxy or fluorine,

C_4-C_6-alkadienylene, optionally substituted by C_1-C_3-alkyl or by 1 or 2 fluorine atoms, and

1,3,5-hexatrienylene, optionally substituted by fluorine,

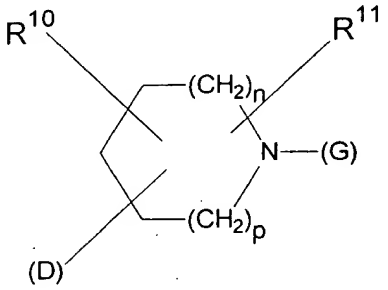
D is selected from C_1-C_8-alkylene, optionally substituted once or twice by methyl or hydroxy,

C_2-C_8-alkenylene, optionally substituted once or twice by methyl or hydroxy, wherein the double bond optionally is to ring E,

C_3-C_8-alkinylene, optionally substituted once or twice by methyl or hydroxy, and

the group consisting of C_1-C_8-alkylene, C_2-C_8-alkenylene and C_3-C_8-alkinylene, wherein one to three methylene units are isosterically replaced by O, S, NH, $N(CH_3)$, $N(COCH_3)$, $N(SO_2CH_3)$, CO, SO or SO_2,

E is



(E1)

wherein

n and

p are, independent of each other, 0, 1, or 2, with the proviso that **n** + **p** = 2,

R10 is selected from hydrogen, C_1-C_3-alkyl, hydroxy, and hydroxymethyl,

R11 is hydrogen or an oxo group which is adjacent to the nitrogen atom,

G is selected from hydrogen, **G1, G2, G3, G4** and **G5**, wherein

G1 represents the residue

$$—(CH_2)_r—(CR^{13}R^{14})_s—R^{12} \qquad (G1),$$

wherein

r is 0, 1 or 2 and

s is 0 or 1,

R^{12} is selected from hydrogen, C_1-C_6-alkyl, C_3-C_8-cycloalkyl, benzyl, phenyl,

the group consisting of benzocyclobutyl, indanyl, indenyl, oxoindanyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, oxotetrahydronaphthyl, biphenylenyl, fluorenyl, oxofluorenyl, anthryl, dihydroanthryl, oxodihydroanthryl, dioxodihydroanthryl, phenanthryl, dihydrophenanthryl, oxodihydrophenanthryl, dibenzocycloheptenyl, oxodibenzocycloheptenyl, dihydrodibenzocycloheptenyl, oxodihydrodibenzocycloheptenyl, dihydrodibenzocyclooctenyl, tetrahydrodibenzocyclooctenyl and oxotetrahydrodibenzocyclooctenyl, bound directly or over a methylene group,

and

the group consisting of furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, imidazothiazolyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, oxoindolinyl, dioxoindolinyl, benzoxazolyl, oxobenzoxazolinyl, benzisoxazolyl, oxobenzisoxazolinyl, benzothiazolyl, oxobenzthiazolinyl, benzoisothiazolyl, oxobenzoisothiazolinyl, benzimidazolyl, oxobenzimidazolinyl, indazolyl, oxoindazolinyl, benzofurazanyl, benzothiadiazolyl, benzotriazolyl, oxazolopyridyl, oxodihydrooxazolopyridyl, thiazolopyridyl,

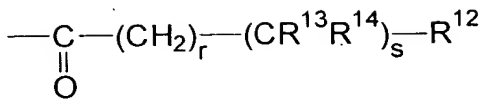
oxodihydrothiazolopyridyl, isothiazolopyridyl, imidazopyridyl, oxodihydroimidazopyridyl, pyrazolopyridyl, oxodihydropyrazolopyridyl, thienopyrimidinyl, chromanyl, chromanonyl, benzopyranyl, chromonyl, quinolyl, isoquinolyl, dihydroquinolyl, oxodihydroquinolinyl, tetrahydroquinolyl, oxotetrahydroquinolinyl, benzodioxanyl, quinoxalinyl, quinazolinyl, naphthyridinyl, carbazolyl, tetrahydrocarbazolyl, oxotetrahydrocarbazolyl, pyridoindolyl, acridinyl, oxodihydroacridinyl, phenothiazinyl, dihydrodibenzoxepinyl, oxodihydrodibenzoxepinyl, benzocycloheptathienyl, oxobenzocycloheptathienyl, dihydrothienobenzothiepinyl, oxodihydrothienobenzothiepinyl, dihydrodibenzothiepinyl, oxodihydrodibenzothiepinyl, octahydrodibenzothiepinyl, dihydrodibenzazepinyl, oxodihydrodibenzazepinyl, octahydrodibenzazepinyl, benzocycloheptapyridyl, oxobenzocycloheptapyridyl, dihydropyridobenzodiazepinyl, dihydrodibenzoxazepinyl, dihydropyridobenzoxepinyl, dihydropyridobenzoxazepinyl, oxodihydropyridobenzoxazepinyl, dihydrodibenzothiazepinyl, oxodihydrodibenzothiazepinyl, dihydropyridobenzothiazepinyl, and oxodihydropyridobenzothiazepinyl, bound directly or over a methylene group,

R^{13} has the same meaning as **R^{12}**, but is selected independently therefrom,

R^{14} is selected from hydrogen, hydroxy, methyl, benzyl, phenyl, and,

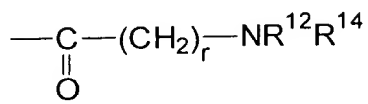
the group consisting of indanyl, indenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, benzofuryl, benzothienyl, indolyl, indolinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, chromanyl, quinolyl, and tetrahydroquinolyl, bound directly or over a methylene group,

G2 is selected from



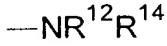
(G2a)

and



(G2b),

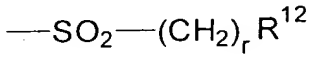
wherein $\mathbf{R^{12}}$ and $\mathbf{R^{14}}$ have the above meanings, or the group



is a nitrogen-containing heterocycle bound over the nitrogen atom, the nitrogen-containing heterocycle being selected from the group consisting of azetidine, pyrrolidine, piperidine, (1H)tetrahydropyridine, hexahydroazepine, (1H)tetrahydroazepine, octahydroazocine, pyrazolidine, piperazine, hexahydrodiazepine, morpholine, hexahydrooxazepine, thiomorpholine, thiomorpholine-1,1-dioxide, 5-aza-bicyclo[2.1.1]hexane, 2-aza-bicyclo[2.2.1]heptane, 7-aza-bicyclo[2.2.1]heptane, 2,5-diaza-bicyclo[2.2.1]-heptane, 2-aza-bicyclo[2.2.2]octane, 8-aza-bicyclo[3.2.1]octane, 2,5-diazabicyclo[2.2.2]octane, 9-azabicyclo[3.3.1]nonane, indoline, isoindoline, (1H)-dihydroquinoline, (1H)-tetrahydroquinoline, (2H)-tetrahydroisoquinoline, (1H)-tetrahydroquinoxaline, (4H)-dihydrobenzoxazine, (4H)-dihydrobenzothiazine, (1H)-tetrahydrobenzo[b]azepine, (1H)-tetrahydrobenzo[c]azepine, (1H)-tetrahydrobenzo[d]azepine, (5H)-tetrahydrobenzo[b]oxazepine, (5H)-tetrahydrobenzo[b]thiazepine, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole, (10H)-dihydroacridine, 1,2,3,4-tetrahydroacridanone, (10H)-phenoxazine, (10H)-phenothiazine, (5H)-dibenzazepine, (5H)-dihydrodibenzazepine, (5H)-octahydrodibenzazepine, (5H)-dihydrodibenzodiazepine, (11H)-

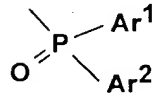
dihydrodibenzo[b,e]oxazepine, (11H)-dihydrodibenzo[b,e]thiazepine, (10H)-dihydrodibenzo[b,f]oxazepine, (10H)-dihydrodibenzo[b,f]thiazepine, and (5H)-tetrahydrodibenzazocine,

G3 is



(G3),

G4 is



(G4),

wherein

Ar^1 and

Ar^2 are selected independently of each other from phenyl, pyridyl, and naphthyl,

G5 is

(G5),

wherein

R^{15} is selected from trifluoromethyl, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, and benzyloxy,

wherein aromatic ring systems optionally are substituted independently of each other by one to three substituents independently selected from the group consisting of halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, C_3-C_8-cycloalkyl, phenyl, benzyl, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkoxy entirely or partially substituted by fluorine; benzyloxy, phenoxy, mercapto, C_1-C_6-alkylthio, carboxy, C_1-C_6-alkoxycarbonyl, benzyloxycarbonyl, nitro, amino, mono-C_1-C_6-alkylamino, and di-(C_1-C_6-alkyl)-amino, wherein two adjacent groups in the ring or ring system optionally form an additional ring over a methylenedioxy bridge.

44. A compound according to claim 43, wherein:

R^1 is selected from hydrogen, halogen, cyano, methyl, trifluoromethyl, hydroxy, methoxy and methoxycarbonyl,

R^2 is hydrogen or halogen,

R^3 is hydrogen,

R^4 is selected from hydrogen, C_1-C_3-alkyl and hydroxy,

k is 0 or 1,

A is selected from C_2-C_6-alkenylene, optionally substituted once or twice by hydroxy or fluorine, or

C_4-C_6-alkadienylene, optionally substituted by one or two fluorine atoms, and

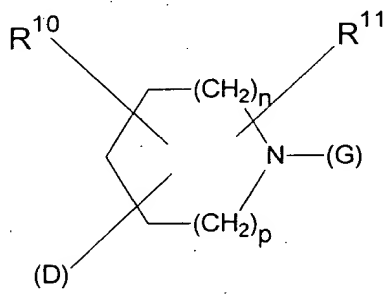
1,3,5-hexatrienylene

D is selected from C_2-C_8-alkylene, optionally substituted by methyl or hydroxy

C_2-C_8-alkenylene, optionally substituted by methyl or hydroxy, wherein the double bond optionally is to ring E, and

the group consisting of C_2-C_8-alkylene and C_2-C_8-alkenylene, wherein one to three methylene units are isosterically replaced by O, NH, $N(CH_3)$, $N(COCH_3)$, $N(SO_2CH_3)$ or CO,

E is



(E1),

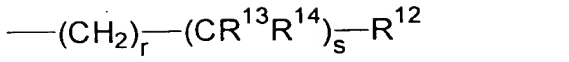
wherein

n and **p** are, independent of each other, 0, 1, or 2, with the proviso that **n** + **p** =2,

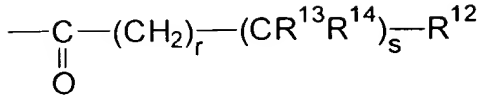
R^{10} is selected from hydrogen, methyl and hydroxyl,

R^{11} is hydrogen or an oxo group adjacent to the nitrogen atom,

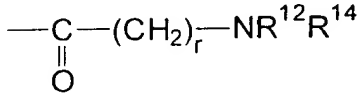
G is selected from hydrogen, C_3-C_8-cycloalkyl, methoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, trifluoroacetyl, diphenylphosphinoyl,



(G1),

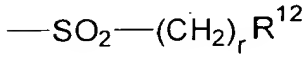


(G2a),



(G2b),

and



(G3),

wherein

r is 0, 1 or 2,

s is 0 or 1,

R^{12} is selected from hydrogen, methyl, benzyl, phenyl,

the group consisting of indanyl, indenyl, oxoindanyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, oxotetrahydronaphthyl, fluorenyl, oxofluorenyl, anthryl, dihydroanthryl, oxodihydroanthryl, dioxodihydroanthryl, dibenzocycloheptenyl, oxodibenzocycloheptenyl, dihydrodibenzocycloheptenyl, and oxodihydrodibenzocycloheptenyl, bound directly or over a methylene group, and

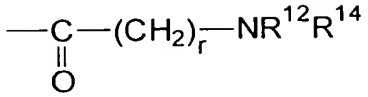
the group consisting of furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, imidazothiazolyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, oxoindolinyl, dioxoindolinyl, benzoxazolyl, oxobenzoxazolinyl, benzisoxazolyl, oxobenzisoxazolinyl, benzothiazolyl, oxobenzthiazolinyl, benzoisothiazolyl, oxobenzoisothiazolinyl, benzimidazolyl, oxobenzimidazolinyl, benzofurazanyl, benzothiadiazolyl, benzotriazolyl, oxazolopyridyl, oxodihydrooxazolopyridyl, thiazolopyridyl, oxodihydrothiazolopyridyl, isothiazolopyridyl, imidazopyridyl, oxodihydroimidazopyridyl, pyrazolopyridyl, thienopyrimidinyl, chromanyl, chromanonyl, benzopyranyl, chromonyl, quinolyl, isoquinolyl, dihydroquinolyl, oxodihydroquinolinyl, tetrahydroquinolyl, oxotetrahydroquinolinyl, benzodioxanyl, quinoxalinyl, quinazolinyl, naphthyridinyl, carbazolyl, tetrahydrocarbazolyl, oxotetrahydrocarbazolyl, pyridoindolyl, acridinyl, oxodihydroacridinyl, phenothiazinyl, dihydrodibenzoxepinyl, benzocycloheptathienyl, oxobenzocycloheptathienyl, dihydrothienobenzothiepinyl, oxodihydrothienobenzothiepinyl, dihydrodibenzothiepinyl, oxodihydrodibenzothiepinyl, dihydrodibenzazepinyl, oxodihydrodibenzazepinyl, octahydrodibenzazepinyl, benzocycloheptapyridyl, oxobenzocycloheptapyridyl, dihydropyridobenzoxepinyl, dihydrodibenzothiazepinyl, and oxodihydrodibenzothiazepinyl, bound directly or over a methylene group,

R^{13} is selected from hydrogen, methyl, benzyl and phenyl,

R^{14} is selected from hydrogen, hydroxy, methyl, benzyl, phenyl, and

the group consisting of naphthyl, furyl, thienyl, oxazolyl, thiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, benzofuryl, benzothienyl, indolyl, indolinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, chromanyl, quinolyl and tetrahydroquinolyl, bound directly or over a methylene group,

wherein in formula



(G2b)

$-NR^{12}R^{14}$ optionally is selected from pyrrolidine, piperidine, (1H)-tetrahydropyridine, hexahydroazepine, octahydroazocine, piperazine, hexahydrodiazepine, morpholine, hexahydrooxazepine, 2-azabicyclo[2.2.1]heptane, 7-azabicyclo[2.2.1]heptane, 2,5-diazabicyclo[2.2.1]heptane, 8-azabicyclo[3.2.1]octane, 2,5-diazabicyclo[2.2.2]octane, indoline, isoindoline, (1H)-dihydroquinoline, (1H)-tetrahydroquinoline, (2H)-tetrahydroisoquinoline, (1H)-tetrahydroquinoxaline, (4H)-dihydrobenzoxazine, (4H)-dihydrobenzothiazine, (1H)-tetrahydrobenzo[b]azepine, (1H)-tetrahydrobenzo[d]azepine, (5H)-tetrahydrobenzo[b]oxazepine, (5H)-tetrahydrobenzo[b]thiazepine, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol, (10H)-dihydroacridine, 1,2,3,4-tetrahydroacridanone, (5H)-dihydrodibenzazepine, (5H)-dihydrodibenzodiazepine, (11H)-dihydrodibenzo[b,e]oxazepine, (11H)-dihydrodibenzo[b,e]thiazepine, (10H)-dihydrodibenzo[b,f]oxazepine and (5H)-tetrahydrodibenzazocine

wherein aromatic ring systems are optionally substituted independently of each other by one to three substituents independently selected from the group consisting of halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, C_3-C_8-cycloalkyl, phenyl, benzyl, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkoxy entirely or partially substituted by fluorine; benzyloxy, phenoxy, mercapto, C_1-C_6-alkylthio, carboxy, C_1-C_6-alkoxycarbonyl, benzyloxycarbonyl, nitro, amino, mono-C_1-C_6-alkylamino, and di-(C_1-C_6-alkyl)-amino, wherein two adjacent groups in the ring or ring system optionally form an additional ring over a methylenedioxy bridge.

45. A compound according to claim 44, wherein:

R^1 is selected from hydrogen, fluorine, chlorine, bromine, methyl, trifluoromethyl and hydroxy,

R^2 and

R^3 are hydrogen,

R^4 is hydrogen or hydroxy,

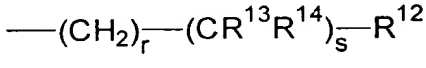
k is 0 or 1,

A is C_2-C_4-alkenylene or 1,3-butadienylene, which are optionally substituted by fluorine,

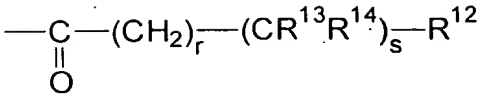
D is selected from C_2-C_6-alkylene, C_2-C_6-alkenylene, wherein the double bond optionally is to ring E, and the group consisting of C_2-C_6-alkylene and C_2-C_6-alkenylene, wherein a methylene unit is isosterically replaced by O, NH, $N(CH_3)$ or CO, or an ethylene group is isosterically replaced by NH-CO or CO-NH, or a propylene group is isosterically replaced by NH-CO-O or O-CO-NH,

E is piperidine, wherein the heterocyclic ring optionally is substituted by an oxo group adjacent to the nitrogen atom,

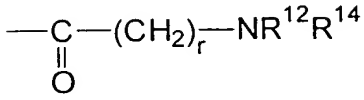
G is selected from hydrogen, tert-butoxycarbonyl, diphenylphosphinoyl,



(G1),

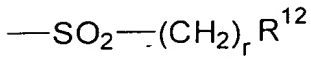


(G2a),



(G2b),

and



(G3),

wherein

r is 0 or 1,

s is 0 or 1,

R^{12} is selected from hydrogen, methyl, benzyl, phenyl,

the group consisting of indenyl, oxoindanyl, naphthyl, tetrahydronaphthyl, fluorenyl, oxofluorenyl, anthryl, dihydroanthryl, oxodihydroanthryl, dioxodihydroanthryl, dibenzocycloheptenyl, and dihydrodibenzocycloheptenyl, bound directly or over a methylene group, and

the group consisting of furyl, thienyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, imidazothiazolyl, benzofuryl, benzothienyl, indolyl, oxoindolinyl, dioxoindolinyl, benzoxazolyl, oxobenzoxazolinyl, benzothiazolyl, oxobenzthiazolinyl, benzimidazolyl, oxobenzimidazolinyl, benzofurazanyl, benzotriazolyl, oxazolopyridyl, oxodihydrooxazolopyridyl, thiazolopyridyl, oxodihydrothiazolopyridyl,

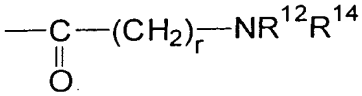
chromanyl, chromanonyl, benzopyranyl, chromonyl, quinolyl, isoquinolyl, oxodihydroquinolinyl, tetrahydroquinolyl, oxotetrahydroquinolinyl, benzodioxanyl, quinazolinyl, acridinyl, oxodihydroacridinyl, phenothiazinyl, dihydrodibenzoxepinyl, benzocycloheptathienyl, dihydrothienobenzothiepinyl, dihydrodibenzothiepinyl, oxodihydrodibenzothiepinyl, dihydrodibenzazepinyl, oxodihydrodibenzazepinyl, octahydrodibenzazepinyl, benzocycloheptapyridyl, oxobenzocycloheptapyridyl, and dihydrodibenzothiazepinyl, bound directly or over a methylene group,

R^{13} is selected from hydrogen, methyl, benzyl and phenyl,

R^{14} is selected from hydrogen, hydroxy, methyl, benzyl, phenyl, and

the group consisting of naphthyl, furyl, thienyl, pyridyl, benzofuryl, benzothienyl, indolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, chromanyl, quinolyl and tetrahydroquinolyl, bound directly or over a methylene group,

wherein in the formula



(G2b)

$-NR^{12}R^{14}$ optionally is selected from pyrrolidine, piperidine, hexahydroazepine, morpholine, 2,5-diazabicyclo[2.2.1]heptane, indoline, isoindoline, (1H)-dihydroquinoline, (1H)-tetrahydroquinoline, (2H)-tetrahydroisoquinoline, (1H)-tetrahydrobenzo[b]azepine, (1H)-tetrahydrobenzo[d]azepine, (5H)-tetrahydrobenzo[b]oxazepine, (5H)-tetrahydrobenzo[b]thiazepine, 1,2,3,4-tetrahydroacridanone, (5H)-dihydrodibenzazepine, (11H)-dihydrodibenzo[b,e]-oxazepine and (11H)-dihydrodibenzo[b,e]thiazepine,

wherein aromatic ring systems optionally are substituted, independently of each other, by one to three substituents which are independently selected from the group consisting of halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, C_3-C_8-cycloalkyl, phenyl, benzyl, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkoxy which is entirely or partially substituted by fluorine; benzyloxy, phenoxy, mercapto, C_1-C_6-alkylthio, carboxy, C_1-C_6-alkoxycarbonyl, benzyloxycarbonyl, nitro, amino, mono-C_1-C_6-alkylamino and di-(C_1-C_6-alkyl)-amino, wherein two adjacent groups on the aromatic ring or ring system optionally form an additional ring over a methylenedioxy bridge.

46. A compound according to claim 45, wherein:

R^1 is selected from hydrogen, fluorine, methyl, trifluoromethyl and hydroxy,

R^2 and

R^3 are hydrogen,

R^4 is hydrogen or hydroxy,

k is 0,

A is ethenylene or 1,3-butadienylene

D is C_2-C_6-alkylene or C_2-C_6-alkenylene, wherein the double bond optionally is to ring E,

E is piperidine,

G is selected from benzyl, phenethyl, fluorenylmethyl, anthrylmethyl, diphenylmethyl, fluorenyl, dihydrodibenzocycloheptenyl, furylmethyl, thienylmethyl, thiazolylmethyl, pyridylmethyl, benzothienylmethyl, quinolylmethyl, phenyl-thienylmethyl, phenyl-pyridylmethyl, dihydrodibenzoxepinyl, dihydrodibenzothiepinyl,

acetyl, pivaloyl, phenylacetyl, diphenylacetyl, diphenylpropionyl, naphthylacetyl, benzoyl, naphthoyl, anthrylcarbonyl, oxofluorenylcarbonyl, oxodihydro-anthrylcarbonyl, dioxodihydroanthrylcarbonyl,

furoyl, pyridylcarbonyl, chromonylcarbonyl, quinolylcarbonyl,

naphthylaminocarbonyl, dibenzylaminocarbonyl, benzylphenylaminocarbonyl, diphenylaminocarbonyl, indolinyl-1-carbonyl, dihydrodibenzazepin-N-carbonyl, tetrahydroquinolinyl-N-carbonyl, tetrahydrobenzo[b]azepinyl-N-carbonyl,

methanesulfonyl, phenylsulfonyl, p-toluenesulfonyl, naphthylsulfonyl, quinolinsulfonyl, and

diphenylphosphinoyl,

wherein aromatic ring systems optionally are substituted independently of each other by one to three substituents which are independently selected from the group consisting of halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, C_3-C_8-cycloalkyl, phenyl, benzyl, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkoxy, entirely or partially substituted by fluorine; benzyloxy, phenoxy, mercapto, C_1-C_6-alkylthio, carboxy, C_1-C_6-alkoxycarbonyl, benzyloxycarbonyl, nitro, amino, mono-C_1-C_6-alkylamino and di-(C_1-C_6-alkyl)-amino, wherein two adjacent groups in the ring or ring system optionally form an additional ring over a methylenedioxy bridge.

47. A compound according to claim 42, which is selected from

N-[4-(1-methylsulfonylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,

N-{4-[1-(2-naphthylsulfonyl)-piperidin-4-yl]-butyl}-3-(pyridin-3-yl)-acrylamide,

N-{4-[1-(2-naphthylsulfonyl)-piperidin-4-yl]-butyl}-5-(pyridin-3-yl)-2,4-pentadienoic acid amide,

N-{4-[1-(1-naphthylaminocarbonyl)-piperidin-4-yl]-butyl}-3-(pyridin-3-yl)-acrylamide,

N-[4-(1-diphenylaminocarbonyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,

N-[4-(1-diphenylaminocarbonyl-piperidin-4-yl)-butyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid amide,

N-{4-[1-(10,11-dihydrodibenzo[b,f]azepin-5-yl-carbonyl)-piperidin-4-yl]-butyl}-3-(pyridin-3-yl)-acrylamide, and

N-[4-(1-diphenylphosphinoyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,

or a pharmaceutically acceptable acid addition salt thereof.

48. A compound according to claim 42, which is selected from

N-[4-(1-acetylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,

N-[4-(1-diphenylacetyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,

N-{4-[1-(3,3-diphenylpropionyl)-piperidin-4-yl]-butyl}-3-(pyridin-3-yl)-acrylamide,

N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,

N-[4-(1-benzoylpiperidin-4-yl)-butyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid amide, and

N-{4-[1-(9-oxo-9H-fluoren-4-yl-carbonyl)-piperidin-4-yl]-butyl}-3-(pyridin-3-yl)-acrylamide,

or a pharmaceutically acceptable acid addition salt thereof.

49. A compound according to claim 42, which is selected from

N-{4-[1-(phenylpyridin-3-yl-methyl)-piperidin-4-yl]-butyl}-3-(pyridin-3-yl)-acrylamide,

N-{4-[1-(phenylpyridin-4-yl-methyl)-piperidin-4-yl]-butyl}-3-(pyridin-3-yl)-acrylamide,

N-{4-[1-(6,11-dihydrodibenzo[b,e]oxepin-11-yl)-piperidin-4-yl]-butyl}-3-(pyridin-3-yl)-acrylamide, and

N-{4-[1-(6,11-dihydrodibenzo[b,e]thiepin-11-yl)-piperidin-4-yl]-butyl}-3-(pyridin-3-yl)-acrylamide,

or a pharmaceutically acceptable acid addition salt thereof.

50. A compound according to claim 42, which is selected from

N-[7-(1-diphenylmethylpiperidin-4-yl)-heptyl]-3-(pyridin-3-yl)-acrylamide,

N-[8-(1-diphenylmethylpiperidin-4-yl)-octyl]-3-(pyridin-3-yl)-acrylamide,

N-[3-(1-diphenylmethylpiperidin-4-yloxy)-propyl]-3-(pyridin-3-yl)-acrylamide, and

N-[3-(1-benzylpiperidin-4-yloxy)-propyl]-3-(pyridin-3-yl)-acrylamide,

or a pharmaceutically acceptable acid addition salt thereof.

51. A compound according to claim 42, which is selected from

N-[2-(1-diphenylmethylpiperidin-4-yl)-ethyl]-5-(pyridin-3-yl)-2,4- pentadienoic acid amide,

N-[4-(1-diphenylmethylpiperidin-4-yl)-butyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid amide,

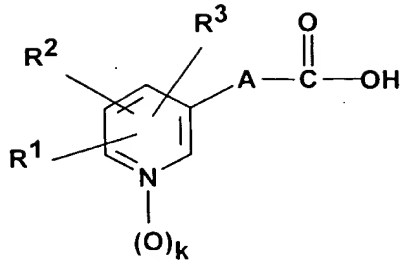
N-[5-(1-diphenylmethylpiperidin-4-yl)-pentyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid amide, and

N-[6-(1-diphenylmethylpiperidin-4-yl)-hexyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid amide,

or a pharmaceutically acceptable acid addition salt thereof.

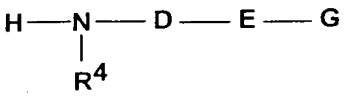
52. A method for the production of compounds according to claim 42, wherein either

(a) carboxylic acids of formula (II)



(II)

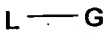
wherein R^1, R^2, R^3, A and k have the meaning given in claim 42 or their reactive derivatives are reacted with compounds of formula (III)



(III)

wherein D, E, G and R^4 have the meanings given in claim 42, or

(b) compounds of formula (I), wherein **G** is hydrogen, are reacted with a compound of formula (IV),



(IV),

wherein **G** has the meaning given in claim 42, with the exception of hydrogen, and **L** represents a suitable nucleofuge or reactive group, whereby the type of specific nucleofuge or reactive group L as well as the reaction conditions are dependent on the nature of the residue **G**, or

(c) compounds of formula (I), wherein **G** is hydrogen, are reacted with a suitable alkylation agent or arylation agent of formula (IV), wherein **G** represents G1, and the nucleofuge L is chlorine, bromine, iodine, or a methanesulfonyloxy-, trifluoromethanesulfonyloxy-, ethanesulfonyloxy-, benzenesulfonyloxy-, p-toluenesulfonyloxy-, p-bromobenzenesulfonyloxy- or m-nitrobenzenesulfonyloxy residue, or an epoxide group, or

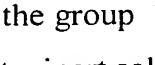
(d) compounds of formula (I), wherein **G** is hydrogen, are reacted with a carboxylic, carbamic, sulfonic or phosphinic acid of formula (V),

(V)

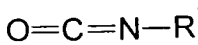
wherein **G** is an acyl, carbamoyl, sulfonyl or phosphinoyl residue or a derivative thereof, selected from symmetric carboxylic acid anhydrides, asymmetric carboxylic acid anhydrides, sulfonic acid anhydrides, acyl halides, sulfonyl halides, carbamoyl halides and phosphinic acids, and the reaction of the acids (V) or their reactive derivatives with the compounds (I), wherein G is hydrogen, optionally occurs in the presence of auxiliary bases in solvents and under conditions as they are described in variant (a), or

(e) compounds of formula (I), wherein **G** is hydrogen are reacted with a carbonyl group transmitter to an intermediate product and the latter, without its purification or previous isolation, is brought to reaction with a primary or secondary amine with the formula (VI)

(VI)

wherein R^{12} and R^{14} and the group  have the meanings according to claim 42, optionally in an absolute, inert solvent in the presence of a tertiary organic amine as an auxiliary base optionally by slowly adding the solution of compounds (I) and the auxiliary base to a solution of an equivalent amount of carbonyl group transmitter, or

(f) compounds of formula (I), wherein **G** is hydrogen, are brought into reaction with an isocyanate of the formula (VII)

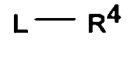


(VII)

wherein R^{12} has the meaning according to claim 42, optionally in pentane, hexane, heptane, benzene, toluene, xylene, dichloromethane, chloroform, 1,2-dichloroethane,

trichloroethylene, diethyl ether, tetrahydrofuran, dioxane, ethyl acetate, butyl acetate, formamide, dimethylformamide, or mixtures thereof, and wherein the reaction temperatures is in the range from -20°C to 150°C, or

(g) compounds of the formula (I), wherein R^4 is hydrogen, are reacted with an alkylation agent of formula (VIII)



(VIII)

wherein R^4 is C_1-C_6-alkyl or C_1-C_6-alkenyl, and L represents chlorine, bromine, iodine, methylsulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy, p-bromobenzenesulfonyloxy or m-nitrobenzenesulfonyloxy, and wherein the reaction is carried out in the presence of tertiary amino groups under the use of a base selected from potassium tert-butylate, sodium hydride, potassium hydride and butyl lithium in pentane, hexane, heptane, benzene, toluene, tetrahydrofuran, dioxane, dimethylsulfoxide, dimethylformamide, or N-methylpyrrolidone, wherein the reaction temperature is between -40°C and 140°C.

53. The method according to claim 52, wherein the reactive derivatives of compound (II) are selected from acid chlorides, p-nitrophenyl esters, 2,4,6-trichlorophenyl esters, pentachlorophenyl esters, cyanomethyl esters, esters of N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxybenzotriazol, N-hydroxypiperidine, 2-hydroxypyridine and 2-mercaptopyridine, chloroformic acid phenyl ester, chloroformic acid benzyl ester, chloroformic acid methyl ester, ethyl ester and isobutyl ester, and wherein the reaction of the compounds (II) with the compounds (III) optionally is performed in the presence of dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride, N,N'-carbonyldiimidazol or 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, wherein

in the case of carbodiimides as a condensation agent, optionally N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxybenzotriazol or N-hydroxypiperidine is added, and

the compounds of formula (III) are submitted to reaction as free bases or in form of their acid addition salts the salts being selected from hydrochlorides, hydrobromides, and sulfates and the reaction of compounds of formula (II), optionally in form of their reactive derivatives, is performed with compounds (III) in benzene, toluene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, trichloroethylene, diethyl ether, tetrahydrofuran, dioxane, glycol dimethyl ether, ethylacetate, acetonitrile dimethylsulfoxide, dimethylformamide or N-methylpyrrolidone, in pure form or as mixtures of two or more thereof, wherein

the reaction is optionally carried out in the presence of sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, triethylamine, ethyldiisopropylamine, tributylamine, N-methylmorpholine, or pydridine, wherein a suitable excess of the compound of formula (III) optionally is used as a base, and in case of use of the compounds of formula (III) in form of their acid addition salts, the amount of the auxiliary base is considered equivalent, and

the reaction temperatures are between -40°C and 180°C .

54. The method according to claim 52, wherein according to method variant **(b)**, the reaction is carried out in benzene, toluene, xylene, tetrahydrofuran, dioxane, glycol dimethyl ether, ethylacetate, acetonitrile, acetone, ethyl methyl ketone, ethanol, isopropanol, butanol, glycol monomethyl ether, dimethylsulfoxide, dimethylformamide or N-methylpyrrolidone, wherein pure solvent or mixtures of two or more of them are used, and the reaction optionally is carried out in the presence of one or more bases selected from sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, triethylamine, ethyldiisopropylamine, tributylamine, N-methylmorpholine and pydridine, and, in the case of the chlorides or bromides as

compounds (IV), optionally sodium iodide or potassium iodide is added and the reaction temperature is in the range of between 0°C and 180°C .

55. A compound according to claim 42, wherein G is hydrogen.

56. A pharmaceutical composition comprising one or more of the compounds according to claim 42 as active ingredient, optionally together with one or more pharmaceutically acceptable carriers, one or more toxicologically safe adjuvants, and optionally in combination with one or more other active ingredients.

57. The pharmaceutical composition according to claim 56, which is

in the form of a tablet, capsule, or coated tablet, optionally in sustained action or gastric fluid-resistant form,

or in the form of a liquid, peroral administration solution, a suspension, or an effervescent tablet,

or in the form of tabs or sachets, optionally in sustained action,

or in gastric fluid-resistant form,

or in the form of a suitable injection or infusion preparation together with suitable pharmaceutically acceptable carriers and adjuvants, optionally in sustained action form or as a parenteral depot medicinal form or implant

or in the form of a concentrate, powder or lyophilisate,

or in the form of an inhalation therapeutic agent, or of a spray together with suitable pharmaceutically acceptable propellants, carriers and adjuvants,

or in the form of a transdermal therapeutic system,

or in the form of a gastrointestinal therapeutic system,

or in the form of a salve, a suspension, an emulsion, a balm or a plaster,

or in the form of a controlled dosage aerosol or of a dry powder dosage formulation,

or in the form of a rectal, genital, or transurethral administration emulsion,

or in the form of a solution, a liposomal solution, an implant, a suppository or a capsule,

or in the form of a nasal, otologic or ophthalmologic composition,

or in a buccally applicable form.

58. A pharmaceutical composition according to claim 56, wherein a dosage unit for single administration contains 0.01 to 2.0 mg or 0.1 to 10 or 20 mg of the active ingredient.

59. A pharmaceutical composition according to claim 56, wherein the pharmaceutically acceptable carrier is a propellant aerosol.

60. The pharmaceutical composition according to claim 59, wherein the propellant aerosol is tetrafluoroethane, heptafluoropropane propane, butane, or dimethyl ether, or a mixture thereof.

61. The pharmaceutical composition according to claim 59, wherein the propellant aerosol contains surface active adjuvants.

62. A pharmaceutical composition according to claim 56, which contains glucose and/or lactose as a dry powder dosage.

63. A pharmaceutical composition according to claim 56, which is present in combination with a further cytostatic agent and/or immunosuppressive agent.

64. A method of treating cancer in the human or animal body comprising administering to the human or animal body an effective amount of a pharmaceutical composition of claim 56.

65. A method of suppressing immunoreactions in the human or animal body comprising administering to the human or animal body an effective amount of a pharmaceutical composition of claim 56.

66. A method of treating cancer in the human or animal body comprising administering to the human or animal body an effective amount of a pharmaceutical composition comprising (E)-3-(3-pyridyl)-N-[2-(1-benzylpiperidine-4-yl)ethyl]-2-propenamide hydrochloride as active ingredient, optionally together with a pharmaceutically acceptable carrier, a toxicologically safe adjuvant, and optionally in combination with other active ingredients.

67. A method of suppressing immunoreactions in the human or animal body comprising administering to the human or animal body an effective amount of a pharmaceutical composition comprising (E)-3-(3-pyridyl)-N-[2-(1-benzylpiperidine-4-yl)ethyl]-2-propenamide hydrochloride as active ingredient, optionally together with one or more pharmaceutically acceptable carriers, one or more toxicologically safe adjuvants, and optionally in combination with one or more other active ingredients.

Supplementary Experimental Data

1. New compounds

Additionally to the compounds already disclosed in Table 2 of the application the applicant has prepared more than 70 new compounds, which all are comprised by the general formula (I) of pending claim 42. Of these, 17 were already disclosed as Examples 52, 53, 66, 71, 102, 122, 126, 145, 158, 160, 174, 184, 204, 208, 217, 227 and 235 in Table 1 of the application as filed. The other 54 new compounds are numbered consecutively by numbers 270 to 328 (numbers 276, 279, 281, and 288 omitted) and are shown in the attached "Supplement for Table 2" (Attachment 1).

2. Pharmacological data

Pharmacological studies have been carried out for all additional 54 compounds and for more than 20 of the compounds already disclosed in Table 2 of the application as filed. The results of all pharmacological studies carried out so far are listed in the provided Attachment 2.

The pharmacological data have been worked out on models which had already been described in the application (Hep G2 cells) or on additional models (Hep G2 cells, A549 cells, HT29 cells, THP-1 cells), described in more detail in Attachment 2 below. The broad effectiveness of the new compounds also was tested in very different human tumor cells, and also the immuno suppressing activity on freshly isolated lymphocytes was investigated.

The results obtained from this large number of data from the pharmacological tests prove that even within the structural variety of compounds claimed the pharmacological activity is given.

In particular, it is shown that the activity of the compounds of formula (I) is maintained even when an extremely large variety of compounds with different functionality in G is used. Even utmost differences in the polarity of the link to E (for example, G1: alkyl or aryl amine, G2 - G5: amide, carbamate, sulphonamide and phosphonamide) do not lead to a disappearance of the activity. Also the introduction of (up to 3) polar heteroatoms with the ability of forming hydrogen bonds is only of a slight influence on the activity. The

same is true, when the ring system G is substituted with one or two residues of highly polar/ionizable or highly lipophilic properties.

The following structural features are now supported by the given examples:

k: 0 (pyridine), 1 (pyridine-N-oxide)

R^1: electron donative and attractive substituents, with different sterical demands, in different pyridine ring-positions

A: vinylene and butadienylene, unsubstituted or substituted with alkyl or ethinylene,

R^4: hydrogen, alkyl, alkenyl, alkoxy, in combination with different groups A and G

D: C_{1-6} and C_8 alkyl chains, and C_{2-8} alkyl chains, wherein 1 to 3 methylene units are isosterically replaced by N, O and/or CO,

G: examples for hydrogen and all subgroups G1 to G5 are provided,

G1: hydrogen, alkyl, aralkyl, heteroarylalkyl, diarylalkyl, and oligocyclic ring systems,

G2: acyl groups, e.g.: formyl, aliphatic, alicyclic, araliphatic, aromatic and heteroaromatic acyl residues with mono-, bi- and tricyclic ring systems of different ring size and with 0 to 3 hetero atoms, and aminocarbonyl groups (ureido groups), wherein the amines are primary, or secondary, aromatic or heterocyclic amines, the ring systems being mono- or tricyclic, with the cyclic secondary amines optionally containing another heteroatom in the ring,

G3: sulphonamides, with aliphatic, aromatic and heteroaromatic mono- or oligocyclic sulphonic acids, with 0 to 3 heteroatoms in the ring,

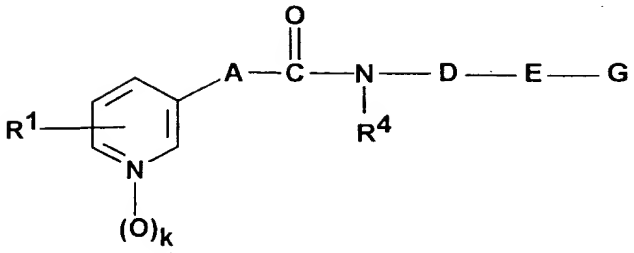
G4: phosphinoyl groups, and

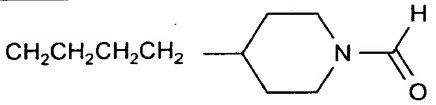
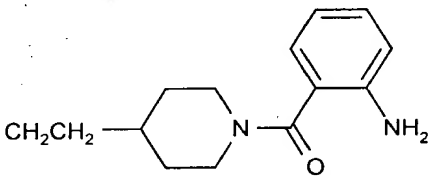
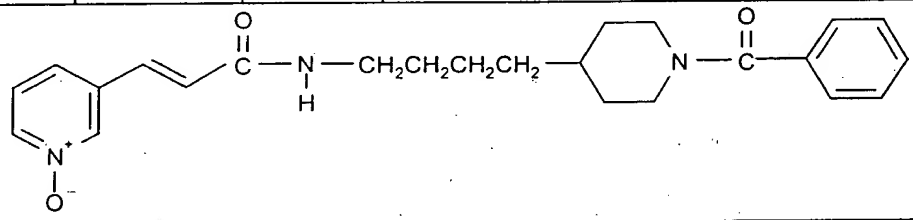
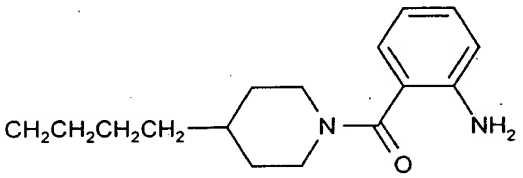
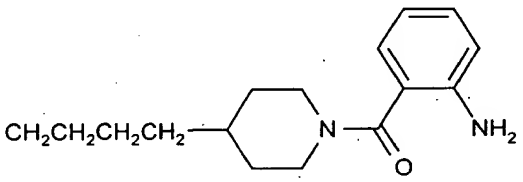
G5: protecting groups, e.g. trifluoroacetyl, ethoxycarbonyl, t-BOC, etc.

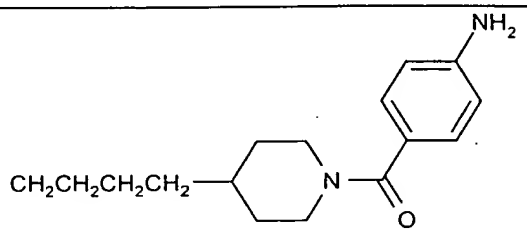
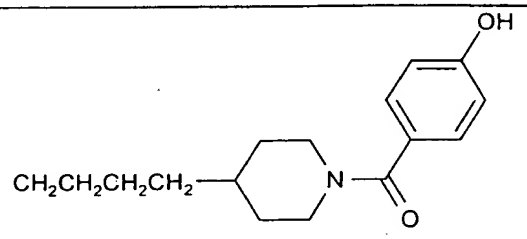
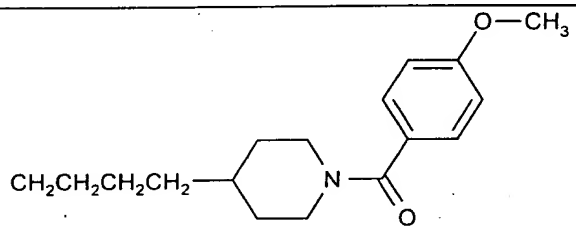
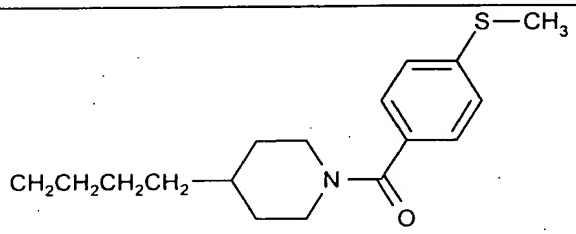
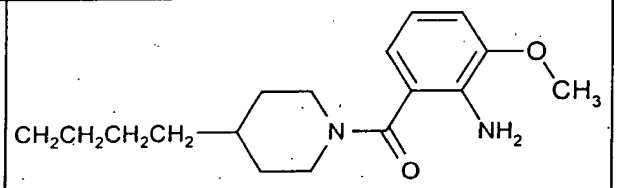
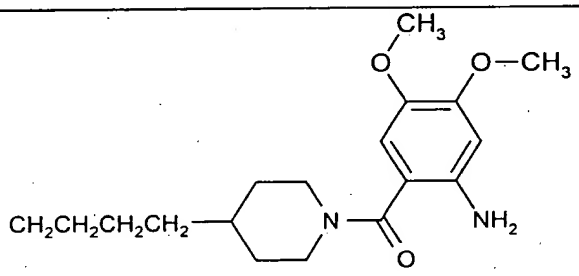
Substituents in G: 1 or 2 substituents which may be the same or different from each other, selected from chlorine, methyl, hydroxy, hydroxymethyl, acetoxy, methoxy, methylthio, nitro, amino, tert-butoxy-carbonylamino, and aminocarbonyl. Several of the carbocyclic and heterocyclic rings carry additional oxogroups.

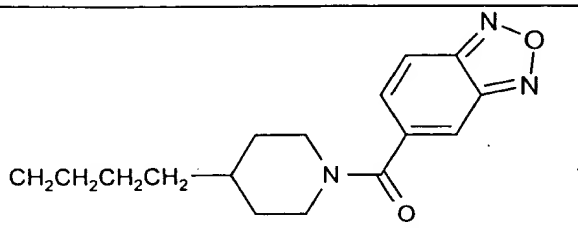
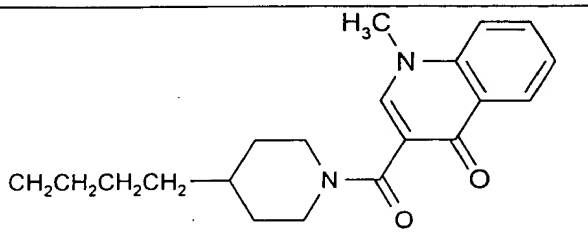
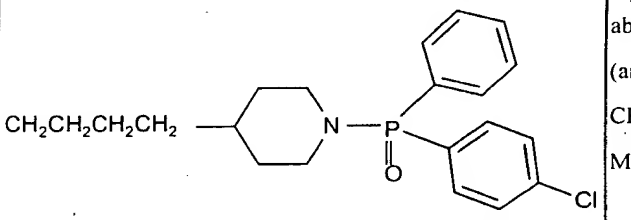
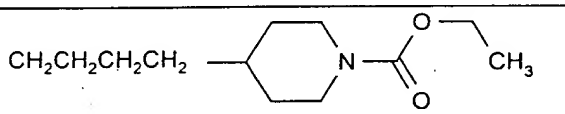
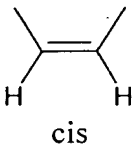
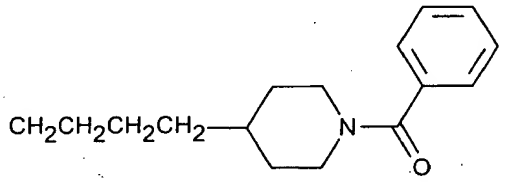
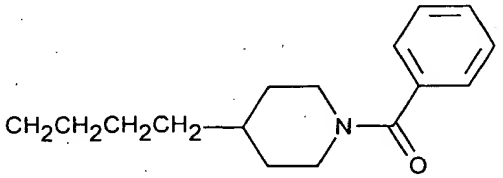
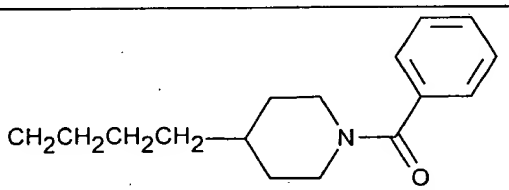
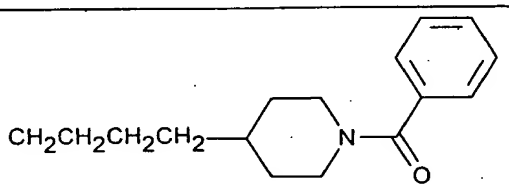
Supplement for
Table 2:

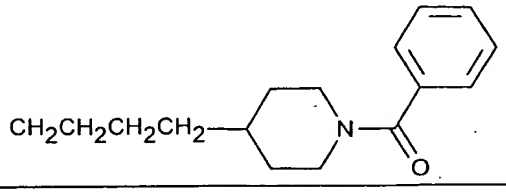
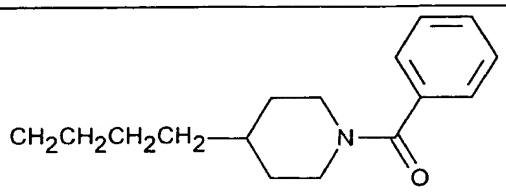
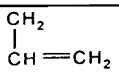
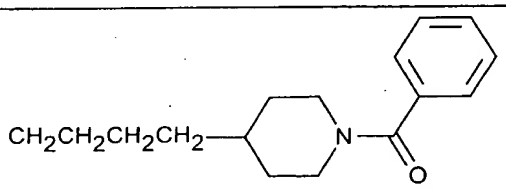
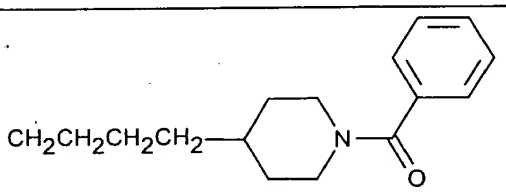
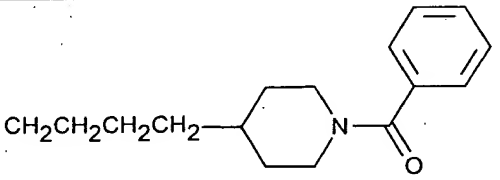
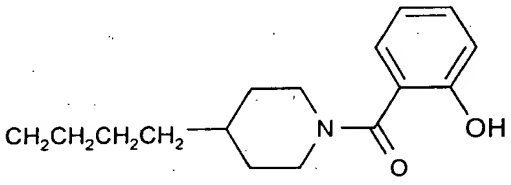
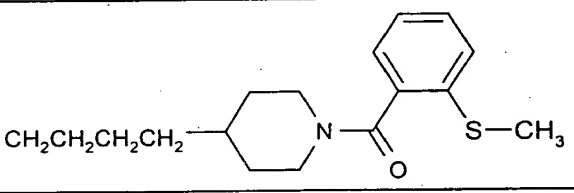
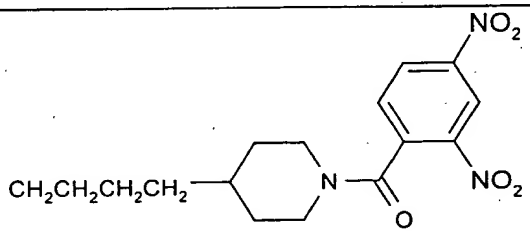
Additionally prepared
compounds of general
formula (I)

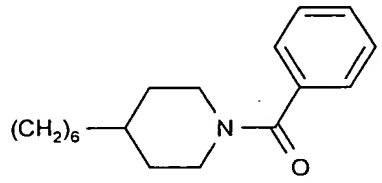
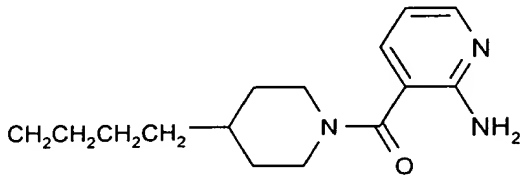
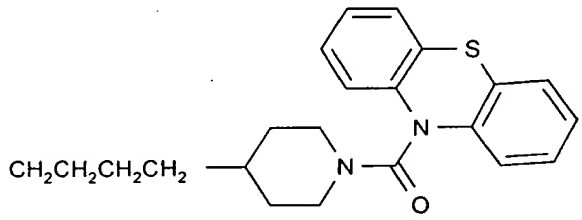
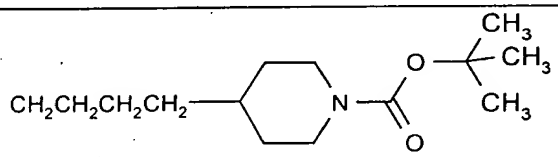
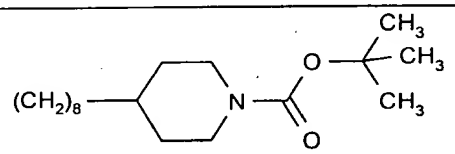
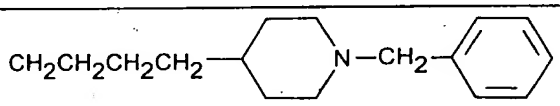
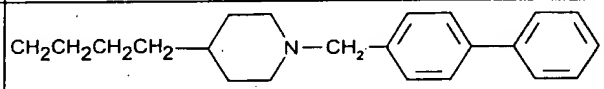
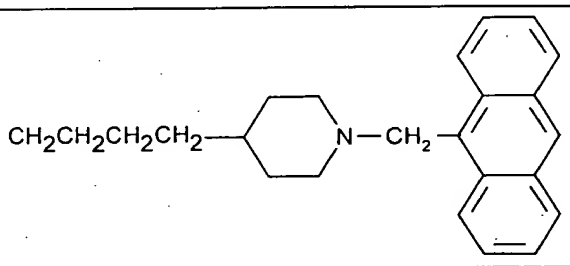


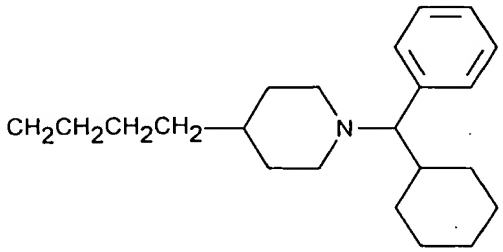
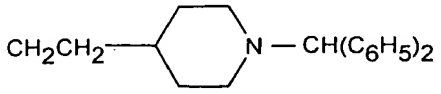
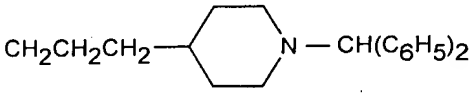
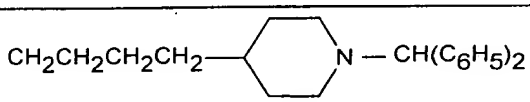
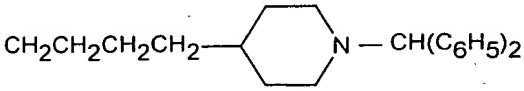
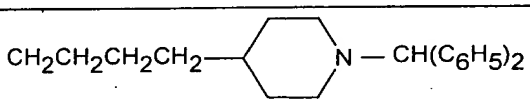
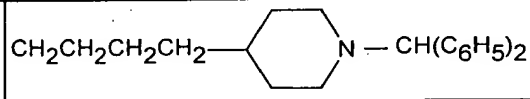
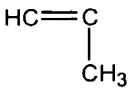
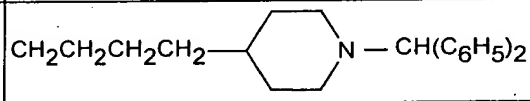
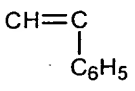
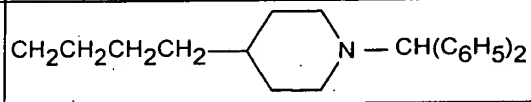
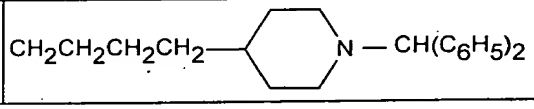
No.	R^1	A	R^4	D–E–G	Mp.[°C][i] (Solvent)
270	H	CH=CH	H		104 (BuCl)
271	H	CH=CH	H		195-196 (MeOH)
272					193 (iPrOH)
273	H	CH=CH	H		120-123 (MeCN)
274	H	CH=CH-CH=CH	H		91-94 (amorphous; EtOH)

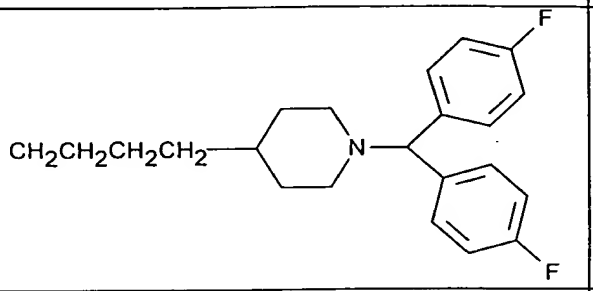
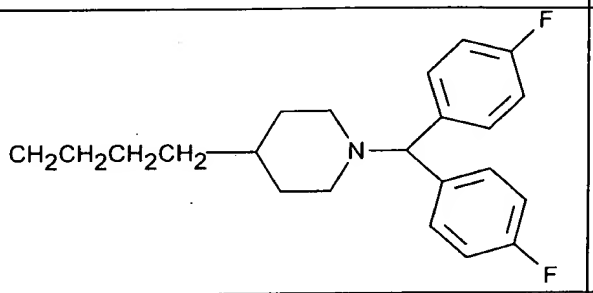
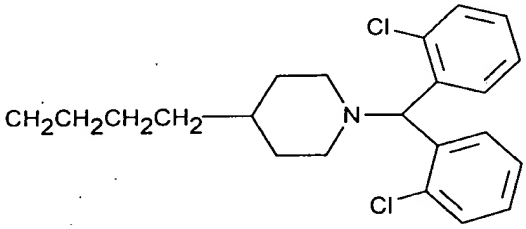
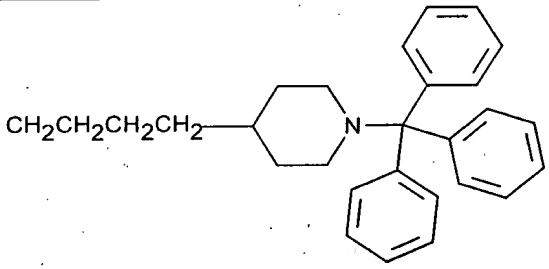
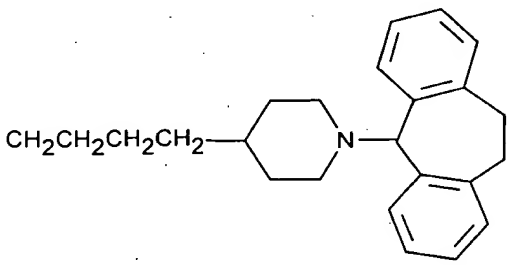
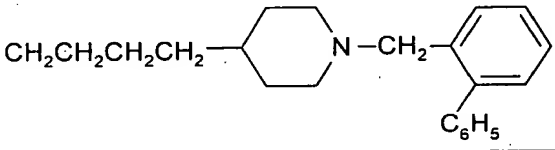
No.	R^1	A	R^4	D–E–G	Mp.[°C][i] (Solvent)
275	H	CH=CH	H		200 (MeCN)
277	H	CH=CH	H		200-205 (EtOH)
278	H	CH=CH	H		111-112 (EE)
280	H	CH=CH	H		98-101 (MeCN/ $CHCl_3$)
282	H	CH=CH	H		Oil
283	H	CH=CH	H		83-85 (MeCN)

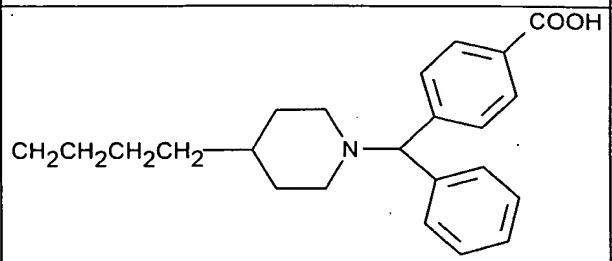
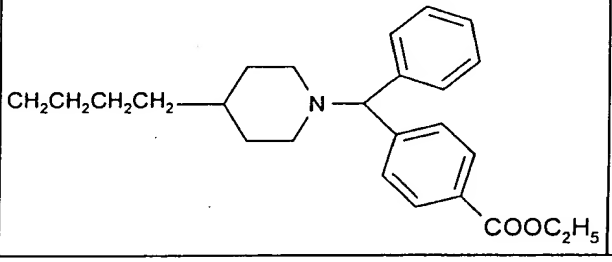
No.	R^1	A	R^4	D–E–G	Mp.[°C][i] (Solvent)
284	H	CH=CH	H		169-170 (iPrOH)
285	H	CH=CH	H		173-175 (EE)
286	H	CH=CH	H		above 65 (amorphous; $CHCl_3$/ $MeOH/NH_3$)
287	H	CH=CH	H		98-99 (MeCN)
289	H	 cis	H		Oil ($CHCl_3$/ MeOH)
290	2-Cl	CH=CH	H		130-131 (MeCN)
291	6-CH_3	CH=CH	H		108-109 (MeCN)
292	6-C_6H_5O	CH=CH	H		57-59 (MeCN)

No.	R^1	A	R^4	D–E–G	Mp.[°C][i] (Solvent)
293	H		H		Oil ($CHCl_3$/ MeOH)
294	H	CH=CH	CH_3		Oil (EE)
295	H	CH=CH			Oil ($CHCl_3$/ MeOH)
296	H	CH=CH	OCH_3		Oil ($CHCl_3$/ MeOH)
297	H	CH=CH-CH=CH	CH_3		Oil (MeCN)
298	H	CH=CH	H		154-155 (2-Butanone)
299	H	CH=CH	H		Resin [ii] ($CHCl_3$/ MeOH)
300	H	CH=CH	H		166 (THF)

No.	R^1	A	R^4	D–E–G	Mp.[°C][i] (Solvent)
301	H	CH=CH	H		109 (CH_2Cl_2/ iPr_2O)
302	H	CH=CH	H		137 (MeCN)
303	H	CH=CH	H		142-143 (MeCN)
304	H	CH=CH	CH_3		Oil ($CHCl_3$/ MeOH)
305	H	CH=CH	H		87-89 (MeCN)
306	H	CH=CH	H		88-90 (MeCN)
307	H	CH=CH	H		147-149 (MeCN)
308	H	CH=CH	H		162-164 (EtOH)

No.	R^1	A	R^4	D–E–G	Mp.[°C][i] (Solvent)
309	H	CH=CH	H		143-145 (MeCN)
310	H	CH=CH	H		141-143 (EE/PE)
311	H	CH=CH	H		110-113 (EE)
312	H	CH=CH	H		156 (EE)
313	2-Cl	CH=CH	H		136-137 (BuCl)
314	6-C_2H_5S	CH=CH	H		158-160 (EE)
315	6-C_6H_5O	CH=CH	H		134-135 (BuCl)
316	H		H		132 (MeOH)
317	H		H		139-140 (MeCN)
318	H	CH=CH	CH_2CH_3		115-117 (iPrOH/iPr_2O)
319	H	CH=CH	$CH_2CH=CH_2$		94-96 (EE)
320	H	CH=CH	H		150-152 (iPrOH)

No.	R^1	A	R^4	D–E–G	Mp.[°C][i] (Solvent)
321	H	CH=CH	H		108 (EE)
322	H	CH=CH	H		79-81 (PE)
323	H	CH=CH	H		129-131 (EE)
324	H	CH=CH	H		150-152 (MeCN)
325	H	CH=CH	H		125-127 (MeCN)
326	H	CH=CH	H		119-121 (BuCl)

No.	R^1	A	R^4	D–E–G	Mp.[°C][i] (Solvent)
327	H	CH=CH	H		108-120 (amorphous, $CHCl_3$/MeOH/ H_2O)
328	H	CH=CH	H		52-58 (amorphous, $CHCl_3$/ MeOH)

i MeOH = methanol
EE = ethylacetate
iPrOH = isopropanol
iPr_2O = diisopropylether
MeCN = acetonitrile
THF = tetrahydrofurane
EtOH = ethanol
Et_2O = diethylether
BuCl = 1-chlorobutane
MTBE = methyl tert-butylether

ii purified by column chromatography

Pharmacological data

1. Growth Inhibition of Human Tumor Cells

The tumor growth inhibiting activity of the substances was determined on human tumor cells in standardized in vitro test systems. In the screening tests, the substances gave IC_{50} values (defined as the concentration in which the cell growth was inhibited by 50%) in a concentration range of 0.1 nM to 10 µM.

Example 1

Hep G2 cells derived from a human liver carcinoma were plated at a density of 20,000 cells/ml in 12-well plastic dishes. Cultivation occurred in Richter's IMEM-ZO nutrient medium with 5% fetal calf serum (FCS) in a tissue culture incubator with a gas mixture of 5% CO_2 and 95% air at a temperature of 37°C. One day after plating, the culture medium was aspirated from the cells and replaced by fresh medium which contained the respective concentrations of the test substances. For the individual concentrations and the controls without test substances, three-fold batches were done for each. Three days after the beginning of treatment, the medium was again renewed with the test compounds. After six days of substance incubation, the test was ended and the protein amount in the individual wells was determined with the sulforhodamine-B-method (according to *P. Skehan et al.: New Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening, J. Natl. Cancer Inst. 82: 1107-1112, 1990*). The IC_{50} values were taken from the dose-response curves and given as a comparative measurement for the activity of the test compounds.

The following results were obtained:

No.	IC_{50} Value [µM]
14	0.2
39	2
40	0.02

No.	IC_{50} Value [μM]
52	3
53	0.07
54	0.6
59	10
62	5
63	10
66	5
70	0.2
71	2
97	1
102	0.05
103	0.07
122	0.05
126	0.05
134	0.007
136	0.002
140	0.002
145	2
150	0.002
151	0.8
153	0.002
158	8
159	0.0005

No.	IC_{50} Value [μM]
160	0.07
162	2
174	0.08
178	0.0007
184	0.0006
195	0.004
199	0.001
200	0.05
208	0.006
217	0.3
219	0.006
230	9
232	0.01
235	0.03
243	5
270	0.008
271	0.4
273	0.0003
274	0.2
275	0.01
277	0.02
278	0.02
280	0.01

No.	IC_{50} Value [μM]
282	0.007
283	0.01
284	0.6
285	0.5
286	0.005
287	0.01
289	0.008
290	1
295	0.3
296	0.4
297	6
298	0.004
299	0.002
300	0.01
301	0.01
302	0.004
303	0.002
305	0.2
306	0.04
307	0.2
308	0.07
309	0.02
310	0.03

No.	IC_{50} Value [μM]
311	0.08
312	0.01
313	7
314	1
315	3
316	0.5
317	2
318	0.8
319	2
320	0.02
321	0.05
322	0.05
323	0.02
324	0.08
325	0.02
326	0.02
327	0.05
328	0.05

Example 2

A549 cells derived from a human liver carcinoma were plated at a density of 20,000 cells/ml in 12-well plastic dishes. Cultivation occurred in Richter's IMEM-ZO nutrient medium with 5% fetal calf serum (FCS) in a tissue culture incubator with a gas mixture of 5% CO_2 and 95% air at a temperature of 37°C. One day after plating the culture medium was aspirated from the cells and replaced by fresh medium which contained the respective concentrations of the test substances. For the individual concentrations and the controls without test substances, three-fold batches were done for each. Three days after the beginning of treatment, the medium was again renewed with the test compounds. After six days of substance incubation, the test was ended and the protein amount in the individual wells was determined with the sulforhodamine-B-method (according to *P. Skehan et al.: New Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening, J. Natl. Cancer Inst. 82: 1107-1112, 1990*). The IC_{50} values were taken from the dose-response curves and given as a comparative measurement for the activity of the test compounds.

The following results were obtained:

No.	IC_{50} Value [µM]
14	2
40	0.5
53	0.09
54	3
62	5
66	6
70	0.5
97	6
102	0.05
103	0.7
122	0.3
126	0.2

No.	IC_{50} Value [μM]
134	0.06
136	0.01
140	0.01
145	2
150	0.005
151	3
153	0.005
158	3
159	0.002
160	0.06
162	8
174	0.07
178	0.002
184	0.004
195	0.01
199	0.002
200	0.3
204	0.8
208	0.01
219	0.1
227	0.002
230	2
232	0.05
235	0.02
270	0.03
271	2

No.	IC_{50} Value [μM]
272	10
273	0.0005
274	2
275	0.08
277	0.07
278	0.02
280	0.02
282	0.008
283	0.02
284	0.2
285	0.2
286	0.02
287	0.01
289	0.007
290	0.7
291	0.7
292	10
293	0.07
294	0.02
298	0.004
299	0.001
300	0.01
302	0.003
304	0.2
305	0.2
306	0.1

No.	IC_{50} Value [μM]
307	0.5
308	0.4
309	0.3
310	0.2
311	0.3
312	0.04
316	5
317	6
318	2
319	5
320	0.1
321	0.2
322	0.1
323	0.03
324	5
325	0.02
326	0.04
327	0.3
328	0.04

Example 3

HT-29 cells derived from a human liver carcinoma were plated at a density of 20,000 cells/ml in 12-well plastic dishes. Cultivation occurred in Richter's IMEM-ZO nutrient medium with 5% fetal calf serum (FCS) in a tissue culture incubator with a gas mixture of 5% CO_2 and 95% air at a temperature of 37°C. One day after plating the culture medium was aspirated from the cells and replaced by fresh medium which contained the

respective concentrations of the test substances. For the individual concentrations and the controls without test substances, three-fold batches were done for each. Three days after the beginning of treatment, the medium was again renewed with the test compounds. After six days of substance incubation, the test was ended and the protein amount in the individual wells was determined with the sulforhodamine-B-method (according to *P. Skehan et al.: New Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening. J. Natl. Cancer Inst. 82: 1107-1112, 1990*). The IC_{50}-values were taken from the dose-response curves and given as a comparative measurement for the activity of the test compounds.

The following results were obtained:

No.	IC_{50}-Value [µM]
54	2
97	2
159	0.0005
306	0.08
312	0.03
321	0.05
325	0.03

Example 4

THP-1 cells derived from a human monocytic leukemia were plated at a density of 200,000 cells/ml in 96-well flat-bottom microtiter plates. Cultivation occurred in RPMI 1640 nutrient medium with 10% fetal calf serum (FCS) in a tissue culture incubator with a gas mixture of 5% CO_2 and 95% air at a temperature of 37°C. For the individual concentrations and the controls without test substances as well as for the background with nutrient medium but without cells, three-fold batches were done for each. After four days of substance incubation 20 µl of WST-1 reagent (Boehringer Mannheim) were pipetted in each individual well. After 30 to 60 minutes of incubation in the tissue culture incubator

at 37°C and 5% CO_2, the light extinction was measured in an ELISA reader at a wave length of 450 nm. The background values were subtracted from the measured values. The IC_{50} values were taken from the dose-response curves and given as a comparative measurement for the activity of the test compounds.

The following results were obtained:

No.	IC_{50} Value [μM]
14	0.04
136	0.005
153	0.0009
159	0.00005
184	0.0005
195	0.008
199	0.0009
219	0.002
270	0.003
271	0.1
273	0.0002
275	0.002
312	0.008
318	0.3
325	0.01

2. Indications

The compounds of formula (I) and their salts permit a therapeutic use in malignant illnesses of humans and animals through their excellent inhibition of the growth of tumor cells. The anti-neoplastic activity of the described substances can be used for prophylactic, adjuvant, palliative, and curative treatment of solid tumors, leukemic illnesses and lymphomas as well as for decreasing or preventing metastasis formation in humans and animals. The therapeutic use is possible in the following illnesses for example: gynaecological tumors, ovarian carcinomas, testicle tumors, prostate carcinomas, skin cancer, kidney cancer, bladder tumors, oesophagus carcinomas, stomach cancer, rectal carcinomas, pancreas carcinomas, thyroid cancer, adrenal tumors, leukemia and lymphomas, Hodgkin's disease, tumor illnesses of the CNS, soft-tissues sarcomas, bone sarcomas, benign and malignant mesotheliomas, but especially intenstine cancer, liver cancer, breast cancer, bronchial and lung carcinomas, melanomas, acute and chronic leukemias. Benign papillomatosis tumors can also be limited in their growth with the named substances. The broad effectiveness of the new compounds were tested for example in very different human tumor cells in vitro according to the methods described in point 1. Thereby, the following exemplary IC_{50} values were obtained for the compounds No. 159 and No. 312, respectively (n.d.: not determined):

Cell Line	Origin	IC_{50} value [µM]	
		No. 159	No. 312
A-204	rhabdomyosarcoma	n.d.	0.02
A549	lung carcinoma	0.002	0.04
Caki-1	kidney clear cell carcinoma	0.002	0.08
Calu-3	lung carcinoma	n.d.	0.05
D257	stomach carcinoma	0.0006	0.07
Hep G2	liver carcinoma	0.0005	0.01
HT-29	colon carcinoma	0.0005	0.02
LNCaP	prostate carcinoma	0.002	0.03

Cell Line	Origin	IC_{50} value [μM]	
		No. 159	No. 312
LoVo	colon carcinoma	n.d.	0.05
MCF-7 M1	ER positive mamma carcinoma	0.0003	0.03
U-87 MG	glioblastoma, astrocytoma	0.006	n.d.
U-373 MG	glioblastoma, astrocytoma	0.002	n.d.
ZR-75-1	ER positive mamma carcinoma	0.002	n.d.
NCI H69	small cell lung carcinoma	n.d.	0.02
Saos-2	osteosarcoma	n.d.	0.03
SK-MEL-2	malignant melanoma	n.d.	0.09
WERI-Rb-1	retinoblastoma	n.d.	0.008
CCRF-CEM	T-cell leukemia	n.d.	0.02
HL-60	promyelocytic leukemia	0.0005	0.05
RPMI 8226	myeloma	n.d.	1
KG-1a	acute myeloblastic leukemia	0.0001	n.d.
THP-1	monocytic leukemia	0.0002	0.008

The novelty of the compounds can be expected to have an independent activity profile in the effectiveness against the various tumor types. Thus, tumors which are resistant to customary cytostatic agents, for example, can respond entirely to these substances. In addition, based on the independent characteristics, combinations of the new compounds with known pharmaceuticals used in chemotherapy are promising as long as their properties are complimented in a suitable manner. The integration of the new structures in a therapy scheme could be successful with one or more substances from the following classes for example: antimetabolites (for example cytarabine, 5-fluorouracil, 6-mercaptopurine, methotrexate), alkylating agents (for example busulfane, carmustine, cisplatin, carboplatin, cyclophosphamide, dacarbazine, melphalane, thiotepa), DNA-intercalating substances and topoisomerase inhibitors (for example actinomycin D, daunorubicin, doxorubicin, mitomycin C, mitoxantrone, etoposide, teniposide,

topotecane, irinotecane), spindle poisons (for example vincristine, navelbine, taxol, taxoter), hormonally active agents (for example tamoxifene, flutamide, formestane, gosereline) or other cytostatic agents with complex modes of action (for example L-asparaginase, bleomycin, hydroxyurea). Resistant tumor cells can be made sensitive again for example by interaction of the new compounds with a mechanism of restistance for common cytostatic agents (for example P-glycoprotein, MRP, glutathione-S-transferase, metallothionein).

3. Immuno Suppressing Activity

Many anti-tumor agents have not only a cytotoxic effect on tumor cells, but also on the blood cell system. This leads to a weakening of the immune defence, which can, in turn, be specifically employed to suppress the rejection reaction after an organ transplantation for example. Also use of the main compounds, optionally in combination with other immunological diseases (for example, psoriasis or autoimmune diseases) seems likely. In order to test the possibility for a therapeutic use in illnesses of this type, the substance activity was tested on freshly isolated lymphocytes as follows:

The spleen of a Swiss mouse served as a lymphocyte source. The lymphocyte population was isolated from the spleen cell suspension over a ficoll gradient and taken up in IMEM-ZO culture medium with 0,1% dextrane 70,000 and 2% fetal calf serum. The cells were plated at a density of ca. 500,000 cells/well/ml in a 12-well plate, 1 ml doubly concentrated test substance solution was pipetted per well and this was subsequently incubated in a tissue culture incubator at 37°C and 5% CO_2. After 2 days, a 1 ml-aliquot with 5 µl of the fluorescent dye solutions propidium iodide (8 mg/ml) and 3,3'-dihexyloxacarbocyanin iodide (40 µg/ml) each was added per well, and incubated for 3 minutes at room temperature. Subsequently, 10,000 cells per each sample were measured on a flow-through cytometer and the percentage amount of vital cells in the population was determined. By means of the dose-response curves, IC_{50}-values were calculated which were also employed in the following Table for the characterization of the individual substances:

No.	IC_{50} Value [μM]
14	0.3
39	4
140	0.02
150	0.0002
153	0.00008
159	0.003
178	0.00006
195	0.003
199	0.00004
219	0.02
270	0.05
273	0.0003
275	0.002
306	0.03
312	0.001
325	0.0008
327	0.003

Furthermore, the independent class of the new compounds also permits a combination with known immunosuppressive agents such as for example cyclosporin A, tacrolimus, rapamycin, azathioprin and glucocorticoids.